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CASE REPORT

Acute kidney injury due to cryoglobulinemic glomerulonephritis as the initial presentation of Chronic Lymphocytic Leukemia: A case report and review of literature

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ABSTRACT

Cryoglobulinemic vasculitis presents with systemic vasculitis including vasculitic rash, fever, peripheral neuropathy, and, in rare cases renal involvement. This could be secondary to infections like hepatitis C, malignancies like myeloma, Non Hodgkin's lymphoma and chronic lymphocytic leukemia. We encountered a patient who presented with fever, anemia, purpuric skin rash and acute kidney injury due to acute glomerulonephritis with nephritic picture and fluid overload that required hemodialysis.Investigations revealed hemolytic anemia, cryoglobulinemia, proliferative glomerulonephritis with Ig M intra-capillary deposits and hyaline thrombi. Bone marrow biopsy clinched the diagnosis of Chronic lymphocytic B cell lymphoma with CD 20 positivity. Treatment was instituted with Rituximab and Bendamustine. Plasmapheresis was done for hyperviscosity syndrome. With treatment, hemodialysis could be discontinued after 10 weeks and renal functions recovered partially with serum creatinine settling at 1.5 mg/dl. We present this case to highlight the presentation of chronic lymphocytic leukemia with cryoglobulinemic vasculitis that presented with purpura and rapidly progressive renal failure that required dialysis.

Introduction

Cryoglobulins (CGs) are antibodies that precipitate in vitro at temperatures less than 37°C and dissolve after rewarming. They have been associated with a variety of diseases, including malignancies, infections, and systemic autoimmune diseases. Cryoglobulinemia has been categorized into three classes: Type I, II, and II. Type I constitutes of a single class of monoclonal immunoglobulins, usually IgM or IgG. Type II is composed of IgG with a Rheumatoid factor IgM of a monoclonal origin. Type III is made of IgG and polyclonal IgM rheumatoid factor. [1]

Cryoglobulinemia often causes systemic vasculitis affecting multiple organs including the nervous system, kidneys, joints, gastrointestinal tract, heart and lungs. The kidneys are a target organ in this disease. Often, there is an underlying aetiology like infections, autoimmune disease or malignancy. The severity of the disease can also range from mild symptoms to a life threatening condition.

Cryoglobulinemia is usually secondary to underlying infections like hepatitis C, autoimmune disease or underlying hematologic malignancies like myeloma, lymphoma and B cell neoplasms. Patients with mixed cryoglobulinemia who do not have a clear underlying cause are classified as essential mixed cryoglobulinemia.

Patient case:

A 39-year-old Ukrainian had been well till six months prior to presentation, when he was diagnosed to have and was treated for hemolytic anemia in his home country. He had undergone a bone marrow biopsy, the report of which was not available. He was commenced on Prednisolone 60mg daily, with improvement in Hb from 6.6 to 9.9g/dl. He presented to our hospital with progressive swelling of legs, shortness of breath and skin rash in lower limbs. History was negative for joint pain, muscle pain or oral ulcers.

Upon examination, Pulse rate was 111 bpm, regular, blood pressure: 170/96 mm hg, temperature: 36.8 C, respiratory rate of 18-20/ mt, SpO2: 100% on room air. Respiratory system examination revealed bilateral crackles. Cardiovascular system examination was remarkable for an S3 gallop. Abdominal examination revealed hepatosplenomegaly. He had a purple purpuric petechial rash on his lower limbs bilaterally along with pitting edema (Fig1). He had no focal neurological deficits.

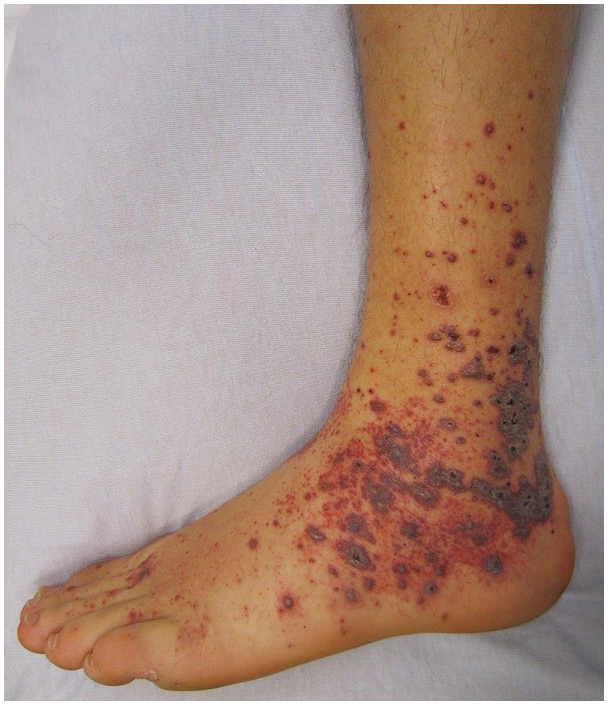

Fig 1: Vasculitic rash on the lower limb.

His initial lab investigations showed:

Laboratory investigation	Value
Hb	6.1g/dl
MCV	77.2fl
WBC	14.5X 103 /cc
Platelets	265X 103/cc
Total bilirubin	0.4 mg/dl
Alkaline phosphatase	82IU/L
ALT	52IU/L
Albumin	3.0g/dl
Globulin	2.1 g/dl
T. protein	5.1 g/dl
Calcium	8.2 mg/dl
Phosphate	8.2 mg/dl
Creatinine	4.1 mg/dl
Urea	294 mg/dl
Sodium	134 mmol/L

Potassium	7 mmol/L
Bicarbonate	13.1mmol/L
Urine routine analysis	Colour: hazy Protein: 2+ WBC: 25-30/ hpf RBC: Numerous/ hpf Blood: 3+ Casts: few granular casts seen
Urine protein/creatinine ratio	489 mg/g
CPK	28 IU/L
LDH	566 IU/L
Ferritin	1123 ng/ml
Iron Saturation	12%
Uric acid	13.2 mg/dl

The clinical impression was that of acute kidney injury secondary to nephritic syndrome and hemolytic anemia. He also had fluid overload, with hyperkalemia and metabolic acidosis.

His resuscitative therapy commenced with intravenous diuretics along with anti-hyperkalemic measures. A temporary right femoral hemodialysis catheter was inserted and he was commenced on hemodialysis. He received 3 units of packed red blood cell transfusion.

Workup:

As part of hemolytic anemia workup, Coomb's test came back negative, as well as G6PD and Paroxysmal Nocturnal hemoglobinuria screens. His Hemoglobin electrophoresis was normal. Blood film revealed marked anisopoikilocytosis with numerous poikilocytes, blister cells, some fragmented cells and polychromatic cells, and a few nucleated red cells. Occasional poikilocyte resembles an incomplete sickle cell. WBC series showed leukocytosis (15,000/ul) with left shift. Platelets were reduced.

With regard to autoimmune workup, his ANA, anti-dsDNA, ENA, ANCA profiles were all negative.

His C3 and C4 were low, at 0.13 (0.9-1.8) and 0.05 (0.1-0.4), respectively. Renal ultraosund showed normal size and a slightly high echogenicity of both kidneys with good cortico-medullary differentiation. No stones, masses or hydronephrosis were observed. In view of the active urinary sediment, the patient was concluded to have Grade I Medical Nephropathy.

In view of nephritic- nephrotic picture with low complements in the setting of skin rash in the lower limbs, serum cryoglobulin was tested, which was reported as strongly positive +++.

In view of the clinical diagnosis of acute nephritic syndrome, he was treated with IV Methylprednisolone 500mg daily for 3 days followed by IV Hydrocortisone.

CT Chest + Abdomen + Pelvis with contrast revealed multiple enlarged mediastinal and retroperitoneal para-aortic lymphadenopathy. Hepatosplenomegaly. Small abdominal ascites. Air space opacities in both lungs likely representing congestive or infective etiology. Moderate bilateral pleural effusions.

Accessing the lymph nodes for a biopsy proved challenging even via interventional radiological or surgical techniques.

During the subsequent hospital stay, the patient developed an episode of hemoptysis and desaturation requiring oxygen supply via non-rebreather mask. A fresh radiological chest image revealed increased size and density of bilateral lung infiltrates, with a higher number on the right side compared to the left. This suggested a suspected case of pulmonary hemorrhage and indicated Goodpasture disease in view of the preceded renal impairment. Anti-GBM antibodies were tested; however, this turned negative.

Patient was maintained on hemodialysis sessions as his renal function and hemolysis were not improving. A renal biopsy was performed in the setting of cryoglobulinemic vasculitis with renal involvement.

Approximately 42 glomeruli were sampled, 1 of which was globally sclerotic. The vast majority of the remaining glomeruli displayed extensive glomerular capillary occlusion by deposits that were strongly PAS positive and Jones to silver negative. These intraluminal deposits ("hyaline thrombi") are segmentally accompanied by intracapillary hypercellularity. (Fig 2a&b). No crescent formation or necrotizing features were identified. Multifocally, arterioles were also shown to be occluded by deposits. Trichrome staining highlighted what appeared to be mild fibrosis. No amyloid was detected with routine stains. Larger caliber arteries were unremarkable.

Fig 2a & b: extensive glomerular capillary occlusion by “hyaline thrombi”

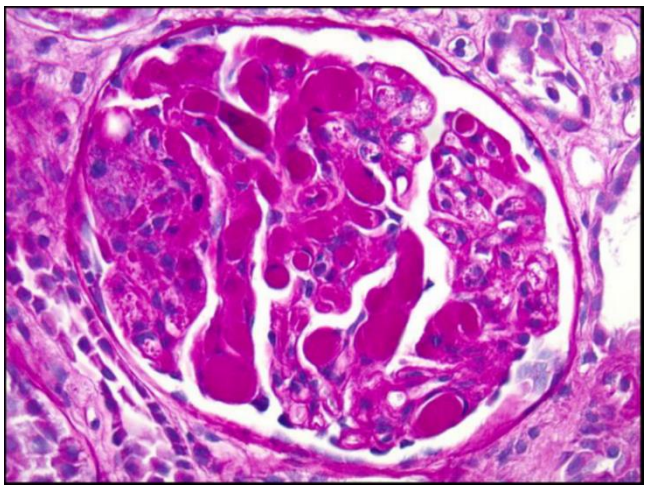

Fig 2a:

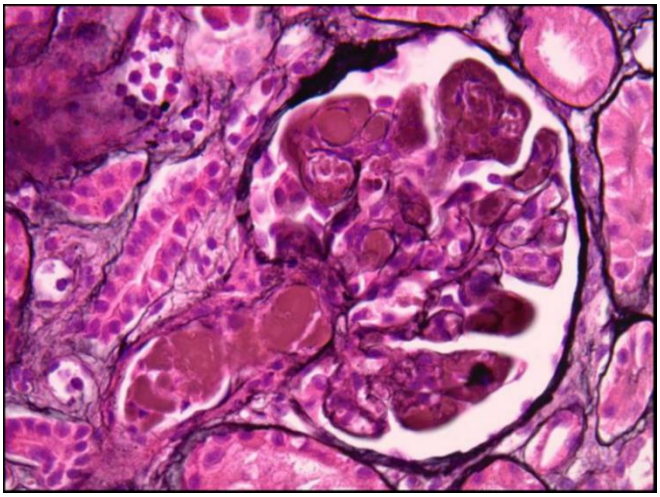

Fig 2b:

Immunofluorescence: Approximately 8 glomeruli were sampled for each reactant tested. Glomeruli displayed prominent intracapillary deposits that stain 4+ for IgM and lambda (Fig 3a and b), 2-3+ for C3 and C1q and are trace to negative for the remaining tested reactants. Finely granular interstitial deposits were also noted for IgM and lambda. Albumin highlights background tissue architecture.

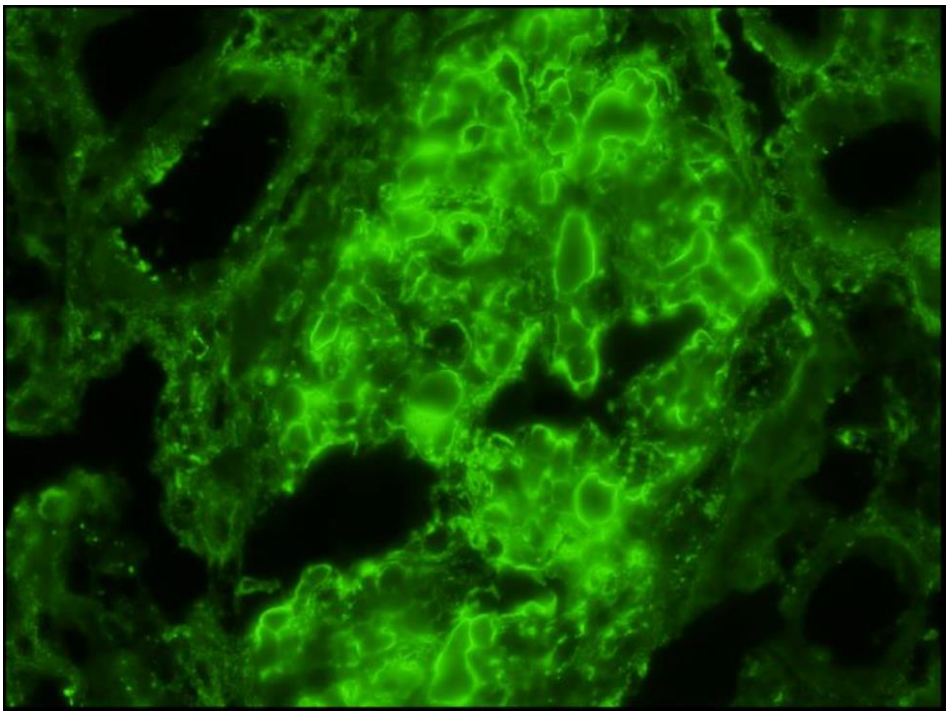

Fig 3a: 4+ positivity for Ig M staining.

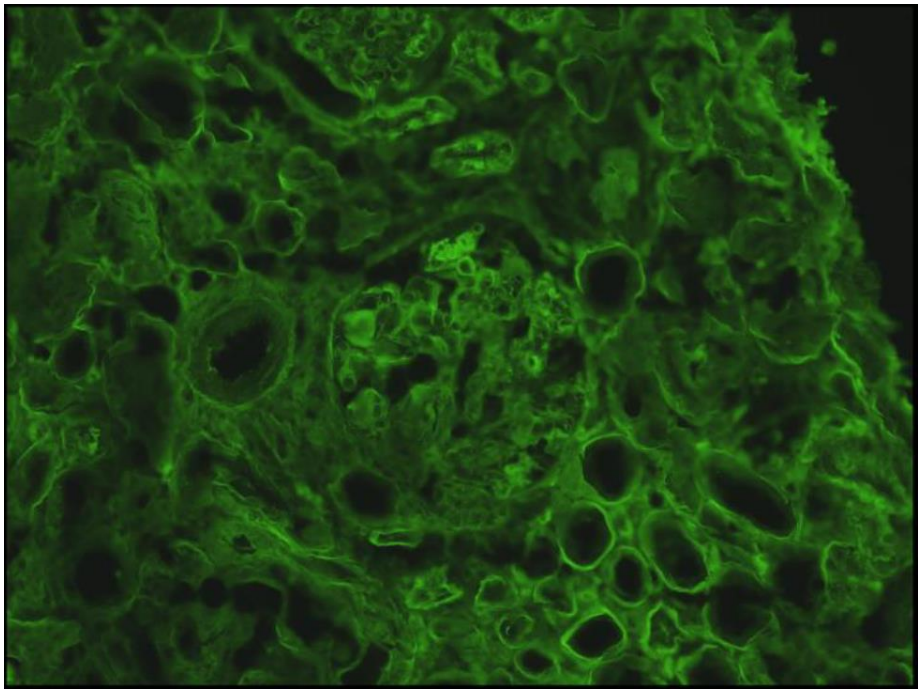

Fig 3b: 4+ positivity for lambda chain of immunoglobulin in the renal biopsy

The picture of monoclonal deposits composed of IgM lambda paraprotein precipitating within glomerular capillaries and associated with glomerular proliferation was highly suggestive of type I cryoglobulinemic glomerulonephritis or Waldenstrom's macroglobulinemia.

Following these findings, a bone marrow biopsy was done.

Bone marrow aspirate smears are an aparticulated and hemolized. Touch imprints show markedly hypercellular marrow spaces which appear packed with almost 100% cellularity. The marrow shows diffuse infiltration by sheets of medium sized lymphoid cells, which are CD20 positive and Ki67 labelling index of less than 1%, with high nucleocytoplasmic ratio and nuclei showing condensed chromatin. These infiltrates comprise about 90% of the total cellularity.

Erythropoiesis and granulopoiesis are markedly suppressed. However, there are foci of adequate, normal appearing megakaryocytes.

Reticulin Stain: Reticulin fibers are increased, MF grade 2-3.

Immunohistochemistry Analysis:

Diffusely and strongly positive for CD20. There is no expression of CD34. Scattered cells are positive with CD3 and CD5. Ki67 expression is seen in less than 1 % of the infiltrating cells.

Cyclin D1: Negative reaction
CD23: Negative reaction
CD43: Negative reaction
CD10: Negative reaction
CD18: Few scattered cells are positive
Bcl2: Faint positive
Bcl6: Negative reaction.

Findings were consistent with bone marrow infiltrated by chronic lymphoproliferative disease, a low-grade B cell neoplasm.

Immunoglobulins analysis
IgG (7.00 - 16.00 g/L) 4.33 Low
IgA (0.70 - 4.00 g/L) 0.18 Low
IgM (0.40 - 2.30 g/L)5.09 High

Free Light Chain KAPPA (3.30 - 19.40 mg/L) 12.88
Free Light Chain LAMBDA (5.71 - 26.30 mg/L) 29,350.00 High

Patient continued to be dialysis dependant. He was diagnosed to have Chronic Lymphocytic leukemia and referred to a haematologist. He was treated with IV Rituximab and Bendamustine. IV Immunoglobulins were also administrated. Prednisolone was tapered to 10mg in six weeks time.

He subsequently developed an episode of confusion and headache with normal findings on CT Brain. This was attributed to hyper-viscosity syndrome, and he received five sessions of plasmapheresis with resolution of symptoms. Chemotherapeutic sessions were complicated by leucopenia, for which he received Granulocyte Colony stimulating factor.

He received monthly cycles of Bendamustine 90mg/ m^2 and Rituximab 375 mg/m^2 for 6 cycles over the next 6 months. He also received prophylaxis with Valganciclocvir and Co-trimoxazole. With these measures there was a considerable improvement in his clinical condition, and the skin rash in the legs disappeared. Ig M levels in the blood normalized. An FDG PET scan done after completion of chemotherapy revealed no evidence of any active hypermetabolic lymph nodes/ lesions in the surveyed whole body.

Hemodialysis sessions were continued for 4 months, and then discontinued as his urine output improved, pedal edema settled and serum creatinine stabilized at 1.3-1.5 mg/dl. Urea was 26 mg/di. Urine protein/ creatinine ratio was 69mg/g. His renal functions during the last follow-up 8 months after initial presentation revealed serum creatinine of 1. 5 mg/di, urea of 26 mg/di.

Subsequently, he travelled to his home country for further follow-up.

Discussion:

Cryoglobulinemia often causes systemic vasculitis, involving the skin and internal organs including the kidney, could be life threatening. Diagnosis of cryoglobulinemia relies on serum cryoglobulin test, in which to ensure that the blood sample temperature is not less than 37°C in the entire pre-analysis phase is the key to avoid false negative results. Cryoglobulinemic vasculitis (Cryo Vas), including cryoglobulinemic glomerulonephritis (Cryo GN), usually occurs in types II and III mixed cryoglobulinemia, and can also be seen in type I cryoglobulinemia caused by monoclonal IgG3 or IgG1. Skin purpura, positive serum rheumatoid factor, and decreased serum levels of C4 and C3 are important clues for prompting types II and III Cryo Vas. Renal biopsy is an important means for diagnosis of Cryo GN, while membranous proliferative GN is the most common pathological type of Cryo GN. [2].

Type I cryoglobulinemia is responsible for about 10-15% of all cryoglobulinemia. Type I cryoglobulinemia is associated with multiple myeloma, non-Hodgkin lymphoma, Waldenstrom macroglobulinemia, chronic lymphocytic leukemia, and monoclonal gammopathy of undetermined significance

[3]. Types II and III cryoglobulinemia are classified as mixed cryoglobulinemia and can be associated with infections, autoimmune diseases, or neoplasms [3]. Type II is commonly associated with infections such as hepatitis C virus, hepatitis B virus, and HIV. Type III is commonly related to autoimmune conditions such as Sjogren syndrome, RA, and systemic lupus erythematosus.

There are two principal mechanisms by which CGs cause disease manifestations. The first mechanism is related to blood stasis due to hyperviscosity and occlusion of small and medium blood vessels due to cryoglobulin precipitation. Such patients frequently develop hyperviscosity syndrome (headache, dizziness, blurry vision, hearing loss, and epistaxis, etc), livedo reticularis, Raynaud phenomena, acrocyanosis, cutaneous necrosis, and ulcers in the distal region of the body (hands, feet, lips, ears, and nose), which often occur or worsen during cold exposure. The above manifestations are common in type I cryoglobulinemia, especially with high concentrations of cryoglobulinemia [2]. Our patient had a skin rash in the lower limbs as a manifestation of cryoglobulinemic vasculitis.

The second mechanism is related with immune-mediated vasculitis of small and medium blood vessel, which is common in types II and III MC, while less prevalent in type I cryoglobulinemia.[2]

Clinical manifestations of cryoglobulinemia span across a wide spectrum of presentations, ranging from indolent courses with favorable prognosis, to more serious presentations vital organ involvement. Symptoms reflect hyperviscosity, due to paraproteinemia, and the underlying pathological process, usually lymphoproliferative disorder. [3] Exposure to cold temperatures predisposes immunoglobulin precipitations, cascading to vasculitis and vessels obstruction. This explains findings such as spontaneous nosebleeds, headaches, blurred vision, purpuric rashes, Raynaud's phenomenon, acrocyanosis, and gangrene. [3]

A percentage of patients may present with major internal organ involvement, including central nervous system, kidneys, and lungs. [4] Cryoglobulinemic vasculitis very commonly involves renal function and could potentially lead to subsequent failure, posing a considerable morbidity and mortality risk in those patients.

Cryoglobulinemic vasculitis frequently involves internal organs including the kidneys. The most common renal manifestation is glomerulonephritis. Membranoproliferative glomerulonephritis is the most common finding on a renal biopsy.

The major clinical presentations include hematuria (almost 100% microscopic hematuria and occasional macroscopic hematuria), proteinuria (almost 100%), hypertension (35%–85%), and chronic renal insufficiency (40%–85% at the time of diagnosis). In addition, 20% to 50% of patients present with nephrotic syndrome and 20% to 30% of patients acute nephritic syndrome. These clinical manifestations are related with the pathological types of cryoglobulinemic glomerulonephritis which are often proliferative GN, especially membrane- proliferative GN [2]. Our patient presented with acute glomerulonephritis with hypertension and microscopic hematuria, associated with acute kidney injury and fluid

overload. The vasculitis rash in his lower limbs, along with hypocomplimentinemia prompted us to consider the diagnosis of cryoglobulinemic vasculitis.

In our patient, the renal biopsy showed proliferative glomerulonephritis with Ig M deposition on immunofluorescence. This is typically seen in Type 1 Cryoglobulinemia. Monoclonal IgM was later confirmed to be due to Chronic Lymphocytic leukemia as revealed on bone marrow biopsy.

Renal limited cryoglobulinemic vasculitis is a subset of essential cryoglobulinemic vasculitis.

In 2018, Toriu N etal described two cases of renal limited cryoglobulinemic vasculitis. The patients had presented with severe nephrotic syndrome and membranoproliferative glomerulonephritis with Ig M deposits on renal biopsy [5]. These patients did not have a favorable response to treatment with Rituximab and only partial response to plasmapheresis and immunosuppressive therapy.

Similar to our patient, Artsiom Klimko reported a patient who presented with acute kidney injury with cryoglobulinemia secondary to hepatic mucosa-associated lymphoid tissue lymphoma. [6]. Recently, Coorey et al described a patient with cryoglobulinemic vasculitis secondary to marginal zone lymphoma in a patient with end stage renal disease on hemodialysis[7].

The improvement of renal function and resolution of skin vasculitic rash after institution of treatment for CLL with anti-CD 20 antibody Rituximab and alkylating agent, Bendamustine demonstrated resolution of cryoglobulinemic vasculitis with treatment of the primary disease. Our patient also developed features of hyperviscosity that required 5 sessions of plasmapheresis. This is typically seen in IgM producing Waldenstroms macroglobulinemia, due to large star-shaped IgM pentamers that are highly viscous [6].

The common causes of death in cryoglobulinemic vasculitis include renal failure, sepsis, cardiovascular disease, hepatic involvement, and lymphoma [8].

Treatment in cryoglobulinemic vasculitis is mainly reserved for symptomatic cases and is targeted at the underlying condition. Rituximab, a B-cell depletion agent, was selected to treat noninfectious cryoglobulinemic vasculitis in our case. According to a Cryovac multicenter survey, rituximab with corticosteroids resulted in greater benefit and was more effective than corticosteroid monotherapy or corticosteroids plus an alkylating agent such as cyclophosphamide in noninfectious cryoglobulinemic vasculitis [10]. Rituximab showed better clinical, renal, and immunologic response with more than 50% reduction in baseline cryoglobulin levels and more than 50% increase in C4 [6]. In our patient Rituximab in addition to being used for resolution of cryoglobulinemic also was used as chemotherapeutic agent in the treatment of B -cell Chronic Lymphocytic Leukemia.

In our patient, plasmapheresis was instituted when he developed features of hyperviscosity syndrome. The indications for plasmapheresis in cryoglobulinemic vasculitis is symptomatic hyperviscosity or life threatening manifestations such as pulmonary haemorrhage. Plasma exchange has also been tried in cases of refractory cryoglobulinemic vasculitis. [7] In their 2019 recommendations, the American Society of Apheresis classified severe/ symptomatic cryoglobulinemia as category II, that is, a category where apheresis is

accepted as a second-line therapy using either plasmapheresis (grade 2A) or immunoadsorption (grade 2B)[11]. Treatment with therapeutic apheresis (Double filtration plasmapheresis or Plasma exchange) for patients with cryoglobulinemic vasculitis is used in cases of severe and/or refractory renal, cutaneous, digestive, cardiac, or neurological involvement. It seems to be important to offer therapeutic apheresis at the beginning to achieve a faster and sustained clinical-biological response, with its duration determined according to the clinical evolution and its frequency guided by the biological parameters (IgM, cryoglobulin, proteinuria, etc.) [12].

In conclusion, we present this case to highlight the multiorgan involvement by cryoglobulinemic vasculitis and to emphasize that secondary causes including underlying hematological neoplasms should be considered as the underlying cause. Treatment of underlying cause, as in our patient, can lead to complete resolution of cryoglobulinemic vasculitis and recovery of even severe acute kidney injury needing hemodialysis is feasible.

Conflicts of Interest Statement:

None

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